AMENDMENT

In the Title:

Delete the title and insert therefor:

B1 -- RECOMBINANT ADENOVIRAL VECTORS FOR HUMAN TUMOR GENE THERAPY AND CELLS CONTAINING THEM--.

REMARKS

Applicants request entry of the amendment, reconsideration of the application, and timely notice of allowability. Claims 20-40 are pending and are being examined.

Applicants amend the title to change the spelling of "tumour" to "tumor" and to better reflect the pending claims. No new matter enters by this amendment.

The Examiner noted that the application papers are incomplete. Applicants will address the issue of Figures 1-5 at a later date. Accordingly, Applicants request that the Examiner hold this issue in abeyance.

I. The Rejection Under 35 U.S.C. §112, First Paragraph

Claims 34-40 stand rejected under 35 U.S.C. § 112, first paragraph, as the specification allegedly fails to provide enablement for the claimed pharmaceutical compositions, methods for preparing cytotoxic T cells *in vivo*, or infected cells. Applicants respectfully traverse this rejection.

The Examiner states three main reasons for this rejection, which Applicants will summarize as: (1) the specification does not provide an enabling disclosure for stimulating

cytotoxic T cell precursors *in vitro* or *in vivo* with any and all cells infected with the recombinant viruses of the invention (*see* pages 3-4 of Paper No. 6); (2) the specification does not provide an enabling disclosure for preparing tumor antigen specific cytotoxic cells *in vivo* for adenoviruses encoding any and all tumor antigens and by any and all routes of delivery to any patient (*see* pages 4-5); and (3) the specification does not provide guidance for the level of tumor antigen specific cytotoxicity T cell stimulation necessary to achieve any therapeutic response. Applicants respectfully disagree. The comments below show that none of these reasons for rejecting claims 34-40 are supported by adequate evidence to one skilled in the art and that the claims are indeed adequately enabled by the specification.

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A. Background and Legal Standards for Examination by the PTO

Initially, applicants point out that the data, especially those shown in Tables 3a, 3b, 4a, and 4b, demonstrate the *in vivo* utility of the adenoviral vectors as recited in the claims and demonstrate a variety of delivery routes for using the vectors. In Tables 4a and 4b, the mice infected with the tumor antigen-containing adenoviruses produced splenic cells capable of specifically detecting and lysing tumor cells (column P511). These are the results irrespective of the delivery route. Clearly, a specific immune response directed to the tumor antigen took place in the animals after the injection or introduction of the adenoviruses. Since one skilled in the art recognizes that cell-based immune reactions encompass cytotoxic T cells, it is logical to conclude that the step of introducing the adenovirus results in cytotoxic T cells being prepared in the mice.

Since there may be some confusion in understanding the data in the specification, applicants request that an Examiner's Interview be granted to discuss the import of the data.

Applicants representative will contact the Examiner approximately one month after the filing of this response to arrange a convenient time.

It is clear that applicants affirmatively state in their application that the adenoviruses of the invention are capable of generating, *in vivo*, an immune reaction specific for cells carrying a tumor antigen (*see* page 8, lines 4-10, and pages 30 –31, for example). In light of these statements and the data, applicants have asserted and shown that the claims are enabled. An applicant's assertions are presumptively correct. As a result, it is the Examiner's burden to provide evidence that one of skill in the art would consider contradictory or inconsistent. *In re Marzocchi,* 169 U.S.P.Q. 367, 370 (C.C.P.A. 1973) ("I]t is incumbent upon the Patent Office . . . to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is *inconsistent* with the contested statement.")

Applicants also note that the standard for the how to use aspect of § 112, first paragraph, for pharmaceutical inventions falls well short of a demonstration of the therapeutic effectiveness that the FDA requires. *In re Brana*, 34 U.S.P.Q.2d 1436, 1442-3 (Fed. Cir. 1995). Any desirable property, even if further research and development may be required, suffices.

B. The First Reason for this Rejection

The Examiner concluded that (1) the specification does not provide an enabling disclosure for stimulating cytotoxic T cell precursors *in vitro* or *in vivo* with any and all cells infected with the recombinant viruses of the invention. The comments at pages 3-4 that allegedly support this reason for the rejection focus on the type of cell that can be selected and the "need" for one or more of a T cell activation signal, IL-2, helper CD4+ T cells, or

professional antigen presenting cells such as dendritic cells and macrophages. Without one of these components, it is asserted that it would have been unpredictable to stimulate T cell precursors.

The compositions of claims 34-36 each recite the adenovirus of claim 20. In Paper No. 6, at page 3, only one "purpose" for these adenoviruses is considered - treating cancer. However, as stated in the specification, the adenoviral vectors of the invention are: capable of transferring and expressing *in vivo* antigens specific to human tumors or melanomas (page 4, line 26 through page 5, line 1, and page 8, lines 4-6); used to cause tumor-specific peptides to be presented at the surface of cells (page 7, line 3-6); and used to make possible the stimulation of CTLs *in vivo* (page 8, lines 6-10, for example). But the Examiner presents no evidence or reasoning that addresses the first two of these expressly stated uses. These claims are enabled if one skilled in the art can make the compositions and use them in any one of these ways or in any way that others in the art would recognize (Revised Examination Utility Guidelines, Federal Register, vol. 62, no. 244, pp. 71440-2). Applicants respectfully submit that the specification clearly shows and states that the recited adenoviruses can be used to express tumor-specific antigens. As nothing contradicts this evidence, a *prima facie* case of lack of enablement has not been made.

In fact, clinical evidence that the compositions as claimed are directly useful as pharmaceuticals exists (*see* the enclosed PCT document WO 00/18933, listed on the enclosed Form 1449). The WO 00/18933 document discusses how vectors containing tumor-specific antigens can be directly injected into patients to retard the progression of cancer. The vectors discussed at Tables 1 and 2 (pages 10-11 of WO 00/18933) appear to directly relate to the recombinant adenoviruses of this invention. Applicants' presumptively useful invention has been

used by one skilled in the art in a manner that encompasses the specifically recited goals of expressing tumor-specific antigens on cells and treating cancer. Claims 34-36, therefore, are enabled by the specification.

Claims 37-40 recite methods for preparing cytotoxic T cells. One of skill in the art, even at the time of filing, was aware of the basic steps of CTL induction. Applicants point to the enclosed excerpt of the text *Fundamental Immunology* (page 967, listed on the enclosed Form 1449). From Fig. 2, mature CTLs can be prepared by processes beginning with macrophages/dendritic cells or by processes beginning with any cell. Accordingly, any cell can be appropriately manipulated to present antigen in a cascade that results in tumor-specific cytotoxic T cells. Indeed, all of the documents the Examiner discusses in this regard (*see* page 3 of Paper No. 6, discussing Gilbert and Fuchs) demonstrate the knowledge one had at hand to accomplish this. One knew of the antigen presenting cell, the dendritic cell, and the cells able to produce T cell activation signals. It follows directly that one skilled in the art could have used any of those cells, or the activation factors available, in the methods of claims 37-40. That dendritic cells may be the optimum choice, as the Examiner suggests at page 4 of Paper No. 6, does not mean that others cells cannot be used.

Furthermore, one skilled in the art could have easily tested any cell infected with the recombinant adenoviruses of the invention for the ability to operate in the methods of claims 37-40. This much is clearly demonstrated by the specification's Examples 4.1, 4.2, and 4.3, where cell lysis tests are presented. That certain cells may not operate to produce tumor-specific cytotoxic T cells, as the comments in Paper No. 6 seem to suggest, is irrelevant. *Atlas Powder Co. v. E. I. du Pont de Nemours & Co.*, 224 U.S.P.Q. 409 (Fed. Cir. 1984). One skilled in the art

can determine, with simple and routine experimentation, what cells can be used to prepare cytotoxic T cells as recited in the claims. That is all the law requires. In fact, the Examiner has not pointed to a specific cell that is considered to be inoperative in the claimed invention. If this rejection is not withdrawn, Applicants respectfully request clarification of what particular cells cannot operate in the claimed invention so that they can address these arguments more particularly.

C. The Second Reason for this Rejection

The Examiner also concluded that (2) the specification does not provide an enabling disclosure for preparing tumor antigen specific cytotoxic cells *in vivo* for adenoviruses encoding any and all tumor antigens and by any and all routes of delivery to any patient (*see* pages 4-5 of Paper No. 6). The discussion at page 4 seems to discount the *in vitro* data because of the presumed lack of costimulation or the alleged differences between *in vitro* and *in vivo* stimulation of T cells and a concern about the ability to stimulate naive T cells.

Although Applicants are unsure of the basis for the Examiner's reasoning, adenovirus clearly causes a specific reaction to tumor cells regardless of the state of activation of any cell involved. Applicant's respectfully submit that one skilled in the art wouldn't reasonably believe a tumor-specific reaction occurred spontaneously. Furthermore, one skilled in the art clearly knows that cytotoxic T cells can be prepared in an animal as a result of challenge with antigen. Indeed, the Bachman *et al.* document seems to address the costimulation issue. At page 323, Bachman states that the costimulatory molecules "crucial" for *in vitro* studies are not needed *in vivo*. "*In vivo* the lack of the same costimulatory molecules or cytokines can apparently be compensated by a redundancy of costimulatory factors which are usually activated during the

infection with a natural mouse pathogen. . . ." There is no evidence that this well known immune cascade does not occur in this case.

The Examiner specifically mentions the Bachman *et al.* document (page 5 of Paper No. 6). However, Bachman merely notes the differences in sensitivity between *in vitro* and *in vivo* studies for a VSV assay. Furthermore, the statements the Examiner refers to in the conclusion, at page 323, relate only to "antiviral function." What that means and if it has any implications on the present invention is not clear. Effects on VSV replication or function are not the focus of applicants' adenoviruses or methods of preparing cytotoxic T cells.

At page 5, the Examiner states that "the majority of mice which were injected in single locations . . . did not produce splenic T cells that demonstrated P1A cytotoxic activity after *in vitro* stimulation." Apparently, the Examiner recognizes that a percentage of mice did actually produce cytotoxic T cells through the use of the methods and adenoviruses claimed. That all the mice did not produce such cells is irrelevant. There is no requirement that any invention be 100% effective under the specific conditions tested. A method for treating cancer that is 20-50% effective is sufficiently enabling and moreover provides significant benefits. Applicants respectfully submit that withholding patent protection to such a method because it is not 90-100% under one set of conditions lacks basis in the applicable laws.

Finally, the Examiner states at page 5 that it is unclear whether the L1210A+ cells used in the assay actually cause the cell lysis in the cytotoxic T cell assays. During the assays noted in the specification, the splenic cells of the mice treated with adenovirus are contacted with the L1210A+ cells. The L1210A+ cells carry a tumor antigen and the lysis of those cells is measured to determine a tumor-specific response. However, exposing the splenic cells to the L1210A+ cells cannot itself cause a rapid *in vitro* generation of cytotoxic T cells that could

confound the interpretation of the results here. One skilled in the art simply would not reasonably consider that as possible and the Examiner provides no reasoning or explanation for how it is possible.

Applicants respectfully request reconsideration.

D. The Third Reason for this Rejection

Finally, the Examiner concluded that (3) the specification does not provide guidance for the level of tumor antigen specific cytotoxic T cell stimulation necessary to achieve any therapeutic response.

Applicants respectfully restate the legal standard appropriate here. An applicant for patent is not required to provide therapeutic or clinical data in order to obtain a patent. As stated in *In re Brana*, the Patent Office must not confuse "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption." *In re Brana,* 34 U.S.P.Q.2d 1436, 1442 (Fed. Cir. 1995). Quoting the C.C.P.A. from *In re Krimmel*, the court in *Brana* stated:

> We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans.

The court continued:

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which the invention in this field becomes useful is well before it is ready to be administered to human. Were we to require Phase II testing in order to prove utility, the associated costs would

> prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.
>
> *In re Brana,* 34 U.S.P.Q.2d 1436, 1442-3 (Fed. Cir. 1995).

At this point it would be inappropriate to deny patent protection to Applicants' invention merely because of a lack of human clinical trial data that correlates with the admittedly successful *in vitro* data. Denial on that basis would prematurely curtail research and development into a promising therapeutic approach to cancer, which the courts recognize as a "crucial" area of research.

In this case, an advance in the approach for preparing cytotoxic T cells specific for cancer tumors suffices. The Examiner does not appear to question that the specification provides an advantageous or desirable approach in the research and development of cancer therapies. Accordingly, as previously held in *Brana*, the PTO should not require additional data here.

Paper No. 6 also mentions a number of documents that apparently address the unpredictability of gene therapy treatments on a therapeutic level. These documents, and the discussion of them, do not address the appropriate standard noted above. Furthermore, even if an invention operates inefficiently, transiently, or in a manner that some consider as needing improvement, it can still satisfy the legal standards of patentability. All that is needed is some desirable property. *In re Brana,* 34 U.S.P.Q.2d 1436, 1442 (Fed. Cir. 1995). The Examiner has not concluded that the invention as claimed completely lacks a desirable property. Therefore, the discussion of how others may feel about efficient, FDA approvable gene therapies is irrelevant.

Paper No. 6 also discusses "further complications" in cancer immunotherapy at page 7, citing Restifo *et al.* While it may be true that some tumors may adapt or escape an induced immune response over time, that does not mean that the methods and compositions used to induce the immune response are not "useful" under the patent laws and the standards

discussed above. Even inventions that provide transient therapeutic benefits can provide a desirable and patentably relevant property.

For these reasons, applicants respectfully submit that this rejection is in error and request its withdrawal.

II. The Rejection Under 35 U.S.C. §112, Second Paragraph

Claims 34-40 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as their invention. Applicants respectfully traverse this rejection.

The Examiner points to the word "preparing" as confusing because it suggests preparing a specific isolated substance (*see* page 8 of Paper No. 6). The dictionary defines "prepare" as "to make ready beforehand for some purpose, use, or activity" (Webster's New Collegiate Dictionary, 10th Edition). Applicants do not suggest that the term "preparing" is confined to this meaning. However, the definition does not suggest or require any isolation or purification process as the Examiner discusses in the rejection. Nowhere does the specification suggest that a specific isolation is required in the inventive methods. Furthermore, the method claims 37-40 recite "preparing cytotoxic T cells" and do not recite patients or animals in which these T cells may be present (see the comments at page 8 of Paper No. 6). Where the cells are when they are prepared according to the method steps would not effect the ability of one skilled in the art to understand these claims.

Applicants request reconsideration and withdrawal of this rejection.

III. The Rejection under 35 U.S.C. § 102(b)

Claims 20-23, 29, and 35-36 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Thai *et al.* (1995) Proc. Am. Assoc. Cancer Res., vol. 36, page 491, abstract # 2927. Applicants respectfully traverse the rejection.

The roughly 150 word abstract cited as the sole basis for this rejection lacks sufficient detail to be anything more than a starting point for further experiments. A potentially anticipatory reference must, from the contents within the four corners of the document itself, enable one skilled in the art to make the claimed invention. Here, the Examiner fails to show how this abstract can possibly enable the claimed invention of claims 20-23, 29, and 35-36. Without such a showing, there can be no *prima facie* case of anticipation.

Furthermore, while the document refers to a MART1 tumor antigen, the word "MART1" does not place a sequence encoding a tumor-specific antigen in the hands of the public. Here, there is no evidence that this MART1 sequence was available to the public. Without a sequence for a tumor-specific antigen, the Zhai document cannot anticipate the invention claimed.

Applicants respectfully submit that a *prima facie* case of anticipation under 35 U.S.C. § 102(b) has not been made. Accordingly, applicants request withdrawal of this rejection.

IV. The Rejections under 35 U.S.C. § 103(a)

Claim 30 stands rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Zhai *et al.* in view of Hadada *et al.* (U.S. Patent 5,891,715). Applicants respectfully traverse the rejection.

This rejection relies on the Zhai document for its alleged teaching of an adenovirus comprising a sequence encoding a tumor-specific antigen. However, as shown above, the Zhai document is not enabled for that alleged teaching. Specifically, Zhai does not enable the production of an adenovirus encoding a tumor-specific antigen. Thus, the Zhai document is not proper prior art for a rejection under 103(a). Without the Zhai document, all of these rejections fail to present a *prima facie* case of unpatentability under 35 U.S.C. § 103(a).

Applicants respectfully request reconsideration and withdrawal of this rejection.

Claims 31-33 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Zhai *et al.* in view of Chen *et al.* (1996) J. Immunology, vol. 156, pp. 224-31.

Claims 24-28, 37, and 39 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Toso *et al.* (1996) Cancer Res., vol. 56, pp. 16-20, in view of Zhai *et al.* and Chen *et al.*

Applicants respectfully traverse these rejections.

All of these rejections rely on the Zhai document for its alleged teaching of an adenovirus comprising a sequence encoding a tumor-specific antigen. However, as shown above, the Zhai document is not enabled for that alleged teaching. Specifically, Zhai does not enable the production of an adenovirus encoding a tumor-specific antigen. Thus, the Zhai document is not proper prior art for a rejection under 103(a). Without the Zhai document, all of these rejections fail to present a *prima facie* case of unpatentability under 35 U.S.C. § 103(a).

In addition, two documents are cited as providing an alleged teaching of an adenoviral vector, Zhai and Chen *et al.*. However, at best, these documents reflect an "obvious to try" situation. Neither present any evidence that the adenoviruses operate in conjunction with

the recited nucleic acid encoding a tumor-specific antigen. The "model tumor-associated antigen" of Chen is β-gal. Calling β-gal a "model" tumor antigen certainly does not make it a tumor antigen. Thus, Chen's discussion of an immune response to β-gal, a bacterial gene, cannot be compared to a response to a tumor antigen.

Accordingly, applicants respectfully submit that these rejections should be withdrawn.

V. Conclusion

Applicants believe that this application is now in condition for allowance. If the Examiner believes that prosecution might be furthered by discussing the application with Applicants' representatives, in person or by telephone, we would welcome the opportunity to do so.

Respectfully submitted,
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